Complete Summary

GUIDELINE TITLE

Assessment: the use of natalizumab (Tysabri) for the treatment of multiple sclerosis (an evidence-based review). Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.

BIBLIOGRAPHIC SOURCE(S)

Goodin DS, Cohen BA, O'Connor P, Kappos L, Stevens JC. Assessment: the use of natalizumab (Tysabri) for the treatment of multiple sclerosis (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008 Sep 2;71(10):766-73. [40 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s)/intervention(s) for which important revised regulatory and/or warning information has been released.

- February 27, 2008, Tysabri (natalizumab): U.S. Food and Drug Administration (FDA) and Biogen Idec, Elan notified healthcare professionals of reports of clinically significant liver injury as early as six days after the first dose of Tysabri. These injuries may lead to death or the need for a liver transplant in some patients. Tysabri should be discontinued in patients with jaundice or other evidence of significant liver injury. Physicians should inform patients that Tysabri may cause liver injury.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **
SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT

CATEGORIES
 IDENTIFYING INFORMATION AND AVAILABILITY
 DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Multiple sclerosis (MS), including:

- Relapsing remitting MS (RRMS)
- Secondary progressive MS (SPMS)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Technology Assessment
Treatment

CLINICAL SPECIALTY

Allergy and Immunology
Internal Medicine
Neurology
Pharmacology
Radiology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the effectiveness and safety of natalizumab in the treatment of multiple sclerosis (MS), and, specifically, address the following six clinical questions:

- Does treatment with natalizumab reduce disease activity in relapsing-remitting MS (RRMS) by clinical and magnetic resonance imaging (MRI) measures?
- Does treatment with natalizumab reduce disease severity in RRMS by clinical and MRI measures?
- How does the efficacy of natalizumab compare with currently available disease-modifying therapies?
- Is natalizumab effective in other clinical types of MS such as secondary progressive MS (SPMS)?
- In patients with RRMS, does the combination of natalizumab with other disease-modifying therapies improve efficacy?
- In patients with MS, how safe is natalizumab, either alone or in combination with other immune-modulating agents?

TARGET POPULATION

Adults with multiple sclerosis

INTERVENTIONS AND PRACTICES CONSIDERED

1. Natalizumab (Tysabri)
2. Interferon beta-1a (Avonex)
3. Other disease-modifying therapies
4. Combination therapies involving natalizumab were considered but not recommended

MAJOR OUTCOMES CONSIDERED

- Clinical activity as assessed by attack rate or attack-free status
- Magnetic resonance imaging (MRI) activity as assessed by gadolinium enhancement, new T2 lesions, or both
- Clinical severity as assessed by confirmed Expanded Disability Status Scale progression
- MRI severity as assessed by total T2 volume (burden) of disease
- Annualized relapse rate
- Relapse-free duration
- Long-term disability
- Adverse effects of treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The MEDLINE and EMBASE databases (1966 to present) were searched in October 2006 under the terms natalizumab and multiple sclerosis (MS) and the reference lists of identified articles were reviewed. These searches identified 316 articles. Only articles reporting results from controlled clinical trials in humans were included in this assessment. Panel members reviewed the abstracts.

NUMBER OF SOURCE DOCUMENTS

Twelve articles, relating to five randomized controlled trials (RCTs), met the inclusion criteria. In addition, a sixth RCT (the GLANCE trial comparing the combination of natalizumab and glatiramer acetate to glatiramer acetate alone) had sufficient data presented for classification.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Classification of Evidence for Therapeutic Intervention

Class I: Randomized, controlled clinical trial with masked or objective outcome assessment in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are required:

a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets b-d above OR a randomized controlled trial in a representative population that lacks one criteria a-d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.*

Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

* Objective outcome measurement: An outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Each panel member read each article and classified the level of evidence for the clinical trials according to the system used by the American Academy of Neurology for therapeutic interventions.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Other

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Classification of Recommendations

Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. (Studies not meeting criteria for Class I – Class III).

* In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if (1) all criteria are met; (2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This evidence-based review was approved by the Therapeutics and Technology Assessment Subcommittee on November 1, 2007; by the Practice Committee on November 11, 2007; and by the American Academy of Neurology Board of Directors on May 13, 2008.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the strength of the recommendations (A, B, C, U) and classification of the evidence (Class I through Class IV) are provided at the end of the "Major Recommendations" field.

Conclusions

1. Natalizumab reduces measures of disease activity such as clinical relapse rate, gadolinium (Gd)-enhancement, and new and enlarging T2 lesions in patients with relapsing multiple sclerosis (MS) (**Class I studies, Level A**).
2. Natalizumab improves measures of disease severity such as the Expanded Disability Status Scale (EDSS) progression rate and the T2-hyperintense and T1-hypointense lesion burden seen on magnetic resonance imaging (MRI) in patients with relapsing MS (**Class I studies, Level A**).
3. The relative efficacy of natalizumab compared to other available disease-modifying therapies is unknown (**Level U**).
4. The value of natalizumab in the treatment of secondary progressive multiple sclerosis (SPMS) is unknown (**Level U**).
5. The SENTINEL trial provides evidence for the value of adding natalizumab to patients already receiving interferon-beta-1a (IFNbeta-1a,) 30 micrograms, intramuscularly (IM) once weekly (**one Class I study, Level B**). It provides no information either about the value of adding IFN-beta therapy to patients already receiving natalizumab in the treatment of relapsing-remitting multiple sclerosis (RRMS) or about the value of continuing IFN-beta therapy once natalizumab therapy is started (**Level U**).
6. There is an increased risk of developing progressive multifocal leukoencephalopathy (PML) in natalizumab-treated patients (**Level A for combination therapy, Level C for monotherapy**). The two cases seen in MS were treated with a combination of natalizumab and IFN-beta-1a, but the fact that PML occurred only with combination therapy may be a chance development. There may also be an increased risk of other opportunistic infections (**Level C**). On the basis of clinical trial data, the PML risk has been estimated to be 1 person for every 1,000 patients treated for an average of 17.9 months, although this estimate could change in either direction with more patient-years of exposure. Since the development of this guideline, two cases of PML have been reported in patients receiving natalizumab monotherapy, one of whom had never previously received any immunomodulatory or immunosuppressive treatment. This observation indicates that natalizumab, by itself, is a risk factor for PML. However, the evidence has not been formally reviewed by the Therapeutics and Technology Assessment Subcommittee (TTA.)

Recommendations

1. Because of the possibility that natalizumab therapy may be responsible for the increased risk of PML, it is recommended that natalizumab be reserved for use in selected patients with relapsing remitting disease who have failed other therapies either through continued disease activity or medication intolerance, or who have a particularly aggressive initial disease course. This recommendation is very similar to that of the U.S. Food and Drug Administration (FDA).
2. Similarly, because combination therapy with IFN-beta and natalizumab may increase the risk of PML, it should not be used. There are also no data to support the use of natalizumab combined with other disease-modifying agents as compared to natalizumab alone. The use of natalizumab in combination with agents not inducing immune suppression should be reserved for properly controlled and monitored clinical trials.

Definitions:

Classification of Recommendations

Level A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

Level B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. (Studies not meeting criteria for Class I–III).

* In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if (1) all criteria are met; (2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

Classification of Evidence for Therapeutic Intervention

Class I: Randomized, controlled clinical trial with masked or objective outcome assessment in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are required:

  a. Concealed allocation
  b. Primary outcome(s) clearly defined
  c. Exclusion/inclusion criteria clearly defined
  d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets b-d above OR a randomized controlled trial in a representative population that lacks one criteria a-d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.*

Class IV: Studies not meeting Class I, II or III criteria, including consensus, expert opinion or a case report.

* Objective outcome measurement: An outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

CLINICAL ALGORITHM(S)

None provided

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

POTENTIAL BENEFITS

Appropriate use of natalizumab to reduce measures of disease activity and improve measures of disease severity in patients with relapsing-remitting multiple sclerosis

POTENTIAL HARMS

- In all six randomized controlled trials of natalizumab, the therapeutic benefits of natalizumab were associated with few notable side effects for up to 2 years of treatment. Nevertheless, 2% to 9% of patients in the AFFIRM and SENTINEL trials had an allergic or other hypersensitivity reaction to natalizumab and in 1%, which included rare anaphylactoid reactions, these were considered serious by the investigators. Also, approximately 6% of patients developed persistent binding antibodies to the natalizumab molecule, and in these patients the therapeutic effect of natalizumab seemed to be neutralized completely.
- Despite such encouraging safety results, there are reasons for caution. After the completion of the SENTINEL trial, two patients (both in the arm receiving combined natalizumab and IFN beta-1a therapy) developed progressive multifocal leukoencephalopathy (PML), one of whom died. The other remains severely disabled. In reviewing the previous experience with natalizumab in Crohn's disease, a third postmortem case of PML was identified in a patient who had received natalizumab alone.
- Although there was not a statistical excess of either opportunistic infections or malignancies in the natalizumab-treated patients, the possibility that these potential complications of therapy may emerge as larger numbers of patients are treated for longer periods of time cannot be excluded at present. At the U.S. Food and Drug Administration hearing for market reapproval, several unusual infections were reported to have occurred in patients receiving natalizumab (either for Crohn's disease or for multiple sclerosis). These included two cases of viral meningitis and encephalitis (one fatal), two cases of acute cytomegalovirus, pulmonary aspergillosis, and one case each of cryptosporidial gastroenteritis, *Pneumocystis carinii* pneumonia, varicella

pneumonia, mycobacterium avium intracellulare complex pneumonia, and *Burkholderia cepacia* pneumonia.

- In assessing the risks and benefits of therapy for individual patients, it must be considered that natalizumab is still a partially effective therapy with very rare but potentially fatal complications, and that multiple sclerosis is typically a nonfatal disease with other therapeutic options not associated with PML.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Quick Reference Guides/Physician Guides
Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

BIBLIOGRAPHIC SOURCE(S)

Goodin DS, Cohen BA, O'Connor P, Kappos L, Stevens JC. Assessment: the use of natalizumab (Tysabri) for the treatment of multiple sclerosis (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008 Sep 2;71(10):766-73. [40 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Sep 2

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Therapeutics and Technology Assessment Subcommittee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: D.S. Goodin, MD; B.A. Cohen, MD, FAAN; P. O'Connor, MD; L. Kappos, MD; J.C. Stevens, MD, FAAN

Therapeutics and Technology Assessment Subcommittee Members: Janis M. Miyasaki, MD, MEd, FAAN (*Co-Chair*); Yuen T. So, MD, PhD (*Co-Chair*); Richard M. Camicioli, MD; Vinay Chaudhry, MD, FAAN; Richard M. Dubinsky, MD, MPH, FAAN; Cynthia L. Harden, MD; Cheryl Jaigobin, MD; Irene L. Katzan, MD; Barbara S. Koppel, MD, FAAN; Kenneth J. Mack, MD, PhD; William H. Theodore, MD, FAAN; James C. Stevens, MD, FAAN

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The American Academy of Neurology (AAN) is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest

forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, *Neurology* peer reviewers and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

Dr. Goodin has received honoraria for lectures or as a consultant (directly or indirectly) from Teva Neuroscience, Biogen/Idec, Merck-Serono, Bayer-Schering Healthcare, and Berlex Laboratories. Dr. Goodin has received research support from Biogen-Idec, Bayer-Schering, and Novartis. Dr. Cohen has received honoraria for lectures or as a consultant (directly or indirectly) from Novartis, Biogen/Idec, Berlex Laboratories, Pfizer, Serono, and Teva Neuroscience. Dr. Cohen also holds equity in Abbott laboratories and Caremark. He estimates that 95% of his clinical effort is devoted to diagnosis and treatment of multiple sclerosis. Dr. O'Connor has received honoraria for lectures or as a consultant (directly or indirectly) from Biogen/Idec, Genzyme, Schering, Serono, Daichi Sankyo, Novartis, BioMS, Abbott, Sanofi Aventis, and Teva Neuroscience. Dr. O'Connor has received research support from Biogen/Idec, Schering, SanofiAventis, Genetech, BioMS, Novartis, and the NIH. He estimates that 25% of his clinical effort is devoted to evoked potentials in MS diagnosis. Dr. Kappos has received research support from the Swiss National Research Foundation, the Swiss MS-Society, Schering AG, Novartis, Biogen/Idec, Sanofi-Aventis, Serono, Centocor, UCB, and Immune Response. Dr. Stevens holds equity in Pfizer.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The use of natalizumab (Tysabri) for the treatment of multiple sclerosis. AAN summary of evidence-based guideline for clinicians. St. Paul (MN): American Academy of Neurology. 2008. 2 p. Available from the AAN Web site.
- The use of natalizumab (Tysabri) for the treatment of multiple sclerosis. Podcast. St. Paul (MN): American Academy of Neurology. 2008. Available from the AAN Web site.

- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the American Academy of Neurology Web site.

PATIENT RESOURCES

The following is available:

- The use of natalizumab (Tysabri) for the treatment of multiple sclerosis. AAN summary of evidence-based guideline for patients and their families. St. Paul (MN): American Academy of Neurology (AAN). 2008. 2 p.

Electronic copies: Available in Portable Document Format (PDF) from the AAN Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI Institute on November 11, 2008. The information was verified by the guideline developer on December 11, 2008.

COPYRIGHT STATEMENT

This NGC summary is based on the original guideline, which is copyrighted by the American Academy of Neurology.

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 1/5/2009